DISSERTATION ON

THE IMPACT OF HIGHLY ACTIVE ANTI RETROVIRAL THERAPY ON CD4 + T CELL COUNT IN PATIENTS WITH ADULT HIV DISEASE

M.D GENERAL MEDICINE

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BONAFIDE CERTIFICATE

Certified that the work "THE IMPACT OF HIGHLY ACTIVE ANTI RETROVIRAL THERAPY ON CD 4 + T CELL COUNT IN PATIENTS WITH ADULT HIV DISEASE" done by Dr.N.D.SOJI, Post Graduate in M.D General Medicine, Tirunelveli Medical College, Tirunelveli is a bonafide work and has been done under my direct guidance and supervision during the period of his study between May 2004 and March 2007

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AIM OF THE STUDY

1. **To determine the effect of HAART on CD4+ T cell count in patients with proven Adult HIV disease**

2. **To determine the sex wise change in CD4 count in patients receiving HAART therapy.**

INTRODUCTION

The dreadly disease Acquired Immune Deficieny Syndrome (AIDS) appeared first around 1970s [11]. The disease had not been recognized until in early 80s when the syndrome of immune deficiency was found to be widely prevalent among homosexuals and IV drug abusers.

Later the cause was found to be a virus and was named Lymphadenopathy Associated Virus [22,39]. Then around 1980 the virus was renamed as Human Immune Deficiency Virus (HIV).

The first case of this disease was reported in 1980, three years after which the disease was named as AIDS. Prior to that the syndrome had several names around the world. Early cases were reported from USA and subsequently the disease started spreading to Africa, Europe and Asia.

The first article on AIDS was published in 1981 authored by Michael Gottleib [6] . The article reported about the unusual infection of Pnemocystis carinii among IV drug abusers. The hunt for the HIV etiology has grown until the etiologic agent HIV belonging to Lentivirus was found.

The discovery of HIV was a milestone in the history of AIDS. Later on elaborate research and studies were conducted and the impact of HIV on human immune system were revealed.

One of the vastly studied materials is the destruction of CD4+ T lymphocytes by HIV , a key factor in the pathogenesis of the disease [1,2,3,59].

The CD4 helper Cells play a major role in the body's immune system. The CD4 cells are undoubtedly much reduced in number with advanced disease and this correlation of CD4 cells and AIDS progression have been studied elaborately by researchers [41].

Nowadyays the disease progression and the emergence of opportunistic infections are predicted by CD4 T helper cell counts. The CD4 cells help to recognise the foreign agents and with the help of other T cell lineages tend to contain the infection and eliminate the infective agents.

By destroying the CD4 cells the HIV gain access to the body without any resistance if at all and cause a varied syndrome. Many of the studies have shown an inverse relationship with CD4 cells and viral load [26,31].

The CD4 counts are the predictors of disease progression and to plan the necessary treatment even though there are other parameters available.

The antiretroviral drugs by eliminating the virions tend to increase the CD4 cells indirectly and this has been proved to a large extent. The invention of HAART has promising effects in modulating the CD4 counts and decreasing the incidence of opportunistic infections especially Tuberculosis in our country.

REVIEW OF LITERATURE

AIDS is a syndrome of diseases following infection with HIV I and or HIV II. HIV is a Retrovirus belonging to the family of Lentivirus And formerly called as Human Lymphotrophic Virus. The replication of the virus occurs predominantly in the lymphatic system.the crucial step in viral invasion is the ligandic attachment of the virion to the CD4 cell receptors using surface glycoproteins, causing a deficient immune system rendering the patient more susceptible to opportunistic infections which is a hallmark of AIDS. The Antiretroviral drugs decrease the viral load and increase the CD4 count

STRUCTURE OF HIV

Using electron microscopy, HIV-1 and HIV-2 resemble each other strikingly. However, they differ with regard to the molecular weight of their proteins, as well as having differences in their accessory genes. Both HIV-1 and HIV-2 replicate in CD4+ T-cells.

HIV-1 viral particles have a diameter of 100 nm and are surrounded by a lipoprotein membrane. Each viral particle contains 72 glycoprotein complexes, which are integrated into this lipid membrane, and are each composed of trimers of an external glycoprotein gp120 and a transmembrane spanning protein gp41. The bonding between gp120 and gp41 is only loose and therefore gp120 may be shed spontaneously within the local environment [51].

Glycoprotein gp120 may also be detected in theserum (Oh 1992) as well as within the lymphatic tissue of HIV-infected patients(Sunila 1997). During the process of budding, the virus may also incorporate different host proteins from the membrane of the host cell into its lipoprotein layer, such as HLA class I and II proteins, or adhesion proteins such as ICAM-1 that may facilitate adhesion to other target cells.

The p24 core antigen contains two copies of HIV-1 RNA. The HIV-1 RNA is part of a protein-nucleic acid complex, which is composed of the nucleoprotein p7 and the reverse transcriptase p66 (RT) [51]. The viral particle contains all the enzymatic equipment that is necessary for replication: a reverse transcriptase (RT), an integrase p32 and a protease p11

Most replication competent retroviruses depend on three genes: *gag*, *pol* and *env*: gag means group-antigen., pol represents polymerase and env is for envelope [25]. The classical structural scheme of a retroviral genome is 5.LTR-gag-pol-env-LTR 3.. The LTR (long terminal region)

The *gag* and *env* genes code for the nucleocapsid and the glycoproteins of the viral membrane; the *pol* gene codes for the reverse transcriptase and other enzymes. The accessory genes, *nef*, *tat* and *rev,* are all produced early in the viral replicationcycle.

Nef **may induce downregulation of CD4 (Aiken 1994) and HLA class I molecules (Collins 1998) from the surface of HIV-1-infected cells, which may represent an important escape mechanism for the virus to evade an attack mediated by cytotoxic CD8+ T-cells and to avoid recognition by CD4+ T-cells.**

Vpr **seems to be essential for viral replication in non-dividing cells such as macrophages.** ***Vpu*** **is important for the virus .budding. process** ***Vif*****-deficient HIV-1 isolates do not replicate in CD4+ T-cells, some T cell lines (non-permissive cells) or in macrophages.**

CD4 as a primary receptor for HIV [1,3,5,41]

CD4 is a 58 kDa monomeric glycoprotein that can be detected on the cell surface of about 60 % of T-lymphocytes, on T-cell precursors within the bone marrow and thymus, and on monocytes and macrophages, eosinophils, dendritic cells and microglial cells of the central nervous system. The extracellular domain of the CD4 on T-cells is composed of 370 amino acids; the hydrophobic transmembrane domain and the cytoplasmic part of CD4 on T-cells consist of 25 and 38 amino acids, respectively.

Within the extracellular part of CD4, four regions D1-D4 have been characterized that represent immunoglobulin-like domains. Residues within the V2 region of CD4 (amino acids 40-55) are important for the bonding of gp120 to CD4 and this region overlaps the part of the CD4 where its natural ligands, HLA class II molecules, bind.

The identification of the gp120 binding site on the CD4 of CD4+ T-cells stimulated attempts to use soluble CD4 (sCD4) to neutralize the circulating virus in patients, the aim being the inhibition of viral spread (Schooley 1990).

However it became evident, that even though laboratory viral isolates were easily neutralized by sCD4,neutralization of primary patient-derived isolates had not been achieved. In contrast, sCD4 was able to induce conformational changes within the viral envelope that promoted the infection of target cells (Bour 1995). CD4 attaches to the T cell receptor complex (TCR) on CD4+ T-cells and binds to HLA class II molecules on antigen-presenting cells.

The binding of gp120 to CD4 is not only a crucial step for viral entry, but also interferes with intracellular signal transduction pathways and promotes apoptosis in CD4+ T-cells (Banda 1992).

The apparent specificity of $CD4^+$ cell infection observed initially, together with the observation that T4 cells are those that are depleted in disease (indeed, the course of disease in the patient is followed by $CD4^+$ cell levels), suggested that CD4 antigen might be the receptor for the virus. This was demonstrated by transfecting CD4 antigen gene into $CD4^-$ human cells and showing that they acquired the property of being able to be infected by HIV.

Postfusion events [2,3,5]

Following membrane fusion the virus core uncoats into the cytoplasm of the target cell. The conversion of viral RNA into proviral DNA, mediated by the viral enzyme reverse transcriptase (RT), occurs in the cytoplasm of the target cell and is a crucial step within the viral replication cycle

Blockade of the RT by the nucleoside inhibitor zidovudine was the first attempt to inhibit viral replication in HIV-1 infected patients. Reverse transcription occurs in multiple steps. After binding of the tRNA primers, synthesis of proviral DNA occurs as a minus-strand polymerization starting at the PBS (.primer binding site.) and extending up to the 5. repeat region as a short R/U5 DNA. The next step includes degradation of RNA above the PBS by the viral enzyme RNAase H and a .template switch. of the R/U5 DNA with hybridization of the R sequence at the RNA end.

Now the full length polymerization of proviral DNA with degradation of the tRNA is completed. Reverse transcription results in double-stranded HIV DNA with LTR regions (.long terminal repeats.) at each end. However, cellular activation is necessary for integration of the proviral HIV DNA into the host cell genome after transportation of the pre-integration complex into the nucleus. Since natural HIV-1 infection is characterized by continuing cycles of viral replication in activated CD4+ T-cells, viral latency in these resting CD4+ T-cells likely represents an accidental phenomenon and is not likely to be important in the pathogenesis of this disease.

This small reservoir of latent provirus in quiescent CD4+ T-cells gains importance, however, in individuals who are treated with HAART, since the antivirals are unable to affect non-replicating proviruses and thus the virus will persist in those cells Macrophages, and activated and quiescent CD4+ T-cells are the main targets of infection.

Permanent viral reservoirs, mainly in macrophages and latently infected CD4+ T-cells, are established in the early phase of infection and probably represent the major obstacle so far to successful eradication of HIV.

During the whole course of infection with HIV-1, the lymphoid tissue represents the principle site of HIV-1 replication. The close cell-cell contact between CD4+ T-cells and antigen-presenting cells, the presence of infectious virions on the surface of the FDC, and an abundant production of proinflammatory cytokines such as IL-1, IL-6 or TNFα promotes the induction of viral replication in infected cells

THE COURSE OF AIDS DISEASE

a) Acute infection

Initially, in the period immediately after infection, virus titer rises and the patient sometimes experiences some mononucleosis-like symptoms (fever, rash, swollen lymph glands). The result is an initial fall in the number of $CD4^+$ cells and a rise in $CD8^+$ cells but the numbers quickly return to normal[27]. Macrophages are also infected; indeed, if acquired sexually, HIV at this stage if usually macrophage-tropic.

b) A strong anti-HIV immune defense

Cytotoxic B and T lymphocytes mount a strong defense and virus is greatly reduced in the circulation. During this period, more than 10 billion new HIV particles are produced each day but they are rapidly cleared. There can be up to 10^2 to 10^7 virus particles per ml of blood. Most of this virus is coming from recently infected proliferating $CD4^+$ cells. The infected cells that are producing this virus are destroyed either by the immune system or by the virus.

However, the rate of production of $CD4^+$ cells can compensate for the loss of cells. Most $CD4^+$ cells at this stage are uninfected. This is the most infectious phase of the disease. Sero conversion occurs between one and four weeks after infection [36].

c) A latent reservoir.

Although mainly cleared from the blood, the virus persists elsewhere such as in the lymph nodes, especially in association with dendritic cells. A small fraction of the productively infected $CD4^+$ cells may survive long enough to revert back to the resting memory state (as do non-infected $CD4^+$ memory cells). These carry a copy of the HIV genome, which remains latent until the cells are reactivated by antigen. These memory cells have a great potential for stability and constitute a reservoir that may be very important in drug-based therapy.

Although the number of HIV particles in the bloodstream falls during clinical latency, the virus is detectable. After the initial peak of virus, the virus reaches a "set point" during latency. This set point predicts the time of onset of clinical disease. With less than 1000 copies/ml of blood, disease will probably occur with a latency period of more than 10 years. With fewer than 200 copies/ml, disease does not appear to occur at all [1]. Most patients with more than 100,000 copies per ml, lose their CD4+ cells more rapidly and progress to AIDS before 10 years. Most patients have between 10,000 and 100,000 copies per ml in the clinical latency phase (unless treated chemotherapeutically).

d) Loss of $CD4^+$ cells and loss of the immune response.

The major reason that the immune system fails to control HIV infection is that the $CD4^+$ T helper cells are the target of the virus. Also dendritic cells present antigen to $CD4^+$ cells and may bring the virus into contact with these cells at the time that they are stimulated to proliferate by antigen [3,5]. There is a relentless decline of $CD4^+$ cells with especially a loss of those specific to HIV, which occurs from the very beginning of infection and is permanent. Near the end stage of AIDS $CD8^+$ cells also decline precipitously.

e) Onset of AIDS.

Eventually, the virus can no longer be controlled as the virus and cytotoxic T ($CD8^+$) cells destroy helper (T4) cells.

As the T4 cells fall below 200 per cu mm, virus titers rise rapidly and immune activity falls off. It is the loss of immune competence that enables normally benign parasites such as fungi or protozoa to cause disease. Once AIDS develops, patients rarely survive more than two years without chemotherapeutic intervention. There is considerable variability at this stage. Some patients with clinical AIDS do survive for several years while others who appear relatively healthy can suddenly succumb to a major opportunistic infection. The patients die from opportunistic infections. It is the onset of HIV-associated neoplasm and opportunistic infections that defines AIDS properly.

A phase of HIV infection, AIDS-related complex (ARC), used to be defined. This is now little used. It is the phase of disease that lacks the neoplasms and opportunistic infections that are the definition of AIDS [58]. Patients at this stage of the disease show weight loss and fatigue together with fungal infections of the mouth, finger and toe nails

Patients undergoing HAART demonstrate a dramatic decrease in the number of productively infected CD4+ T cells within the lymphoid tissue (Tenner-Racz 1998).During the natural course of HIV-1 disease, the number of CD4+ T-cells slowly decreases while plasma viremia rises in most patients.

Rosenberg and his group were able to demonstrate that initiation of HAART during primary HIV infection was associated with persistence of an HIV-specific CD4+ Tcell response that was not detected in patients analyzed during the chronic stage of disease (Rosenberg 1997).

Recent studies of subjects infected with human immunodeficiency virus (HIV-1) have produced conflicting results about the extent of reconstitution possible in the $CD4^+$ lymphocyte repertoire after highly active antiretroviral therapy [1,3] (HAART).

The effect of HAART on the incidence of opportunistic infections will probably depend on reconstitution of antigen-specific $CD4^+$ lymphocyte responses to important pathogens, including cytomegalovirus (CMV), the leading cause of blindness in AIDS [4,6]. Several studies have demonstrated an important role for $CD4^+$ lymphocytes in controlling CMV replication in vitro and in clinical studies [7,13].

It is now possible to quantitate antigen-specific $CD4^+$ lymphocyte responses by flow cytometry [14]. Using this method, we studied CMV-specific $CD4^+$ lymphocyte responses in individuals infected with HIV-1 with and without a history of active CMV-associated end organ disease (EOD), and in those with quiescent CMV EOD after ganciclovir therapy and HAART. The presence of active CMV-associated EOD strongly correlated with loss of CMV-specific lymphocyte responses ($P = 0.0004$).

In contrast, patients with no history of CMV-associated EOD and most patients with quiescent EOD after HAART demonstrated strong CMV-specific $CD4^+$ lymphocyte responses.

These data indicate that the loss of CMV-specific $CD4^+$ lymphocyte responses in individuals infected with HIV-1 who have active CMV EOD may be restored after ganciclovir therapy and HAART, which provides evidence for functional immune reconstitution to an important pathogen.

Highly active antiretroviral therapy (HAART) increases CD4(+) cell numbers, but its ability to correct the human immunodeficiency virus (HIV)-induced immune deficiency remains unknown. A three-phase T cell reconstitution was demonstrated after HAART, with: (i) an early rise of memory CD4(+) cells, (ii) a reduction in T cell activation correlated to the decreasing retroviral activity together with an improved CD4(+) T cell reactivity to recall antigens, and (iii) a late rise of "naive" CD4(+) lymphocytes while CD8(+) T cells declined, however, without complete normalization of these parameters [25,47]. Thus, decreasing the HIV load can reverse HIV-driven activation and CD4(+) T cell defects in advanced HIV-infected patients.

A study was conducted and revealed the proportion of patients with CD4 cell counts <50 cells × 10^6/l decreased in response to HAART and the rate of change was greatest between 1 and 3 months after commencing treatment . However, the reduction in patients with a detectable HIV viral load was seen almost immediately after the start of HAART This trend tapers out around 9 months for CD4 counts and around 3 months for HIV viral load measurements. The above changes demonstrate a good response to treatment although some patients have persistently low CD4 cell counts and detectable HIV viral load [33,26] . From a clinical standpoint, only five AE were observed during the

second year of follow up and none during the last year of follow up , indicating significant clinical immunorestoration beyond 12-18 months for all patients. Other clinical and laboratory studies also suggest significant immunorestoration to CMV in response to HAART. Some patients, however, have a persistently low CD4 cell count (<20) following triple therapy and may remain at relatively high risk of developing AIDS diseases. It would therefore seem logical to monitor closely patients with very low CD4 counts after PI initiation and to continue with anti-CMV therapy until CD4 cell counts have been greater than 100 for at least 6 months.

HAART

The development of antiretroviral therapy has been one of the most dramatic progressions in the history of medicine. Zidovudine was first tested on humans in 1985, and introduced as a treatment in March 1987 with great expectations [19,47].

Initially, at least, it did not seem to be very effective. The same was true for the nucleoside analogs zalcitabine, didanosine and stavudine, introduced between 1991 and 1994.

Then, in September 1995, the preliminary results of the European-Australian DELTA Study (Delta 1995) and the American ACTG 175 Study (Hammer 1996) attracted attention. It became apparent that combination therapy with two nucleoside analogs was more effective than monotherapy. All these efforts led to a fast track approval, between December 1995 and March 1996, for all three PIs . first saquinavir, followed by ritonavir and indinavir . for the treatment of HIV. HAART began to spread irreversibly.

By June 1996, the first non-nucleoside reverse transcriptase inhibitor, nevirapine, was licensed, and a third drug class introduced. Nelfinavir, another PI, also arrived.

Antiretroviral agents [13,28,29,30]

Several distinct classes of drugs are now used in combination to treat HIV infection, commonly referred to as HAART, "Highly Active Antiretroviral Therapy"

Nucleoside-Analog Reverse Transcriptase Inhibitors (NRTI). These drugs inhibit viral RNA-dependent DNA polymerase (reverse transcriptase) and are incorporated into viral DNA (they are chain-terminating drugs).

Zidovudine (AZT = ZDV) first approved in 1987

Didanosine (ddI)

Zalcitabine (ddC)

Stavudine (d4T)

Lamivudine (3TC)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). In contrast to NRTIs, NNRTIs are not incorporated into viral DNA; they inhibit HIV replication directly by binding non-competitively to reverse transcriptase.

Nevirapine , Delavirdine

Protease Inhibitors. These drugs are specific for the HIV-1 protease and competitively inhibit the enzyme, preventing the maturation of virions capable of infecting other cells, e.g:

Saquinavir first approved in 1995

Ritonavir

Indinavir

Nelfinavir

Abacavir

Clinical categories in HIV-infected persons [11]

Category A

Asymptomatic HIV infection
Acute (primary) HIV infection with accompanying illness or history of acute HIV infection
Persistent generalized lymphadenopathy

Category B

Symptomatic conditions* that are not included among conditions listed in clinical Category C. Examples include, but are not limited to:
Bacillary angiomatosis
Candidiasis, oropharyngeal (thrush)

Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy

Cervical dysplasia (moderate or severe)/ cervical carcinoma in situ

Constitutional symptoms, such as fever (38.5° C) or diarrhea lasting longer than 1 month

Hairy leukoplakia, oral

Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome

Idiopathic thrombocytopenic purpura

Listeriosis

Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess

Peripheral neuropathy

Category C - AIDS-defining illnesses**

Candidiasis of bronchi, trachea, or lungs

Candidiasis, esophageal

Cervical cancer, invasive*

Coccidioidomycosis, disseminated or extrapulmonary

Cryptococcosis, extrapulmonary

Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)

Cytomegalovirus disease (other than liver, spleen, or nodes)

Cytomegalovirus retinitis (with loss of vision)

Encephalopathy, HIV-related

Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis

Histoplasmosis, disseminated or extrapulmonary

Isosporiasis, chronic intestinal (greater than 1 month's duration)

Kaposi's sarcoma

Lymphoma, Burkitt's (or equivalent term)

Lymphoma, immunoblastic (or equivalent)

Lymphoma, primary, of brain

Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary

Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)

Mycobacterium, other species or unidentified species, disseminated or extrapulmonary

Pneumocystis pneumonia

Pneumonia, recurrent*

Progressive multifocal leukoencephalopathy

Salmonella septicemia, recurrent

Toxoplasmosis of brain

Wasting syndrome due to HIV

The Retroviral agents that are used in this study are

Stauvudine

Lamivudine

Nevirapine

Efavirenz

Zidovudine

The combinations of these drugs are used as HAART therapy in this study.They are;

A. d4T 30 + 3TC + NVP

B. d4T 40 + 3TC + NVP

C. d4T 30 + 3TC + EFV

D. d4T 40 + 3TC + EFV

E. ZDV + 3TC + NVP

F. ZDV + 3TC + EFV

The choice of combinations are based on the disease presentation, emergence of toxicity or side effects, treatment failure, concurrent administration of other drugs which interfere with the metabolism and compliance of the patient.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study was conducted on the patients who attended the ART centre at Tirunelveli Medical College between the period October 2005 and August 2006. The study population consist of all patients with Adult HIV Disease (according to World Health Organisation classification criteria). Patients taking anti-tuberculous drugs are also included in the study. Children are not included in the study.

A total of 58 patients were registered for the study but two of them died during the course of therapy. The net total number of subjects are 56. Among them 43 were males and 13 were females.

A chart was prepared with details regarding initial CD4 count, follow up CD4 count, oppurtunistic infections at the time of presentation, type of HAART therapy and the pre and post therapy body weight.

The diagnosis of AIDS was made using WHO criteria for Adult HIV disease and ELISA test for HIV I&II.

The presence of opportunistic infections were not considered to be interfering with the study and infact they served as prognostic indicators for the HAART.

The initial and follow up CD4 counts were done at atleast six months interval.

Statistical analysis:

The results are inferred on the basis of statistical tools viz., 'Z' test and students 't' test.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

This study was conducted on the patients who attended the ART centre at Tirunelveli Medical College between the period October 2005 and August 2006.The study was a prospective study. A total of 56 patients were studied

Out of the 56, 43 are males and 13 were females

Age Group	Male	Female	Total
20- 29	5	3	8
30- 39	23	8	31
40 – 49	8	0	8
50- 59	5	2	7
60- 69	2	0	2
Total	43	13	56
Mean	39.4	35.8	38.6
S.D	10.1	9.5	10.0
Z	1.17		
Significance	P > 0.05		

The mean age of male patients were 39.4 +/-10.1 and the mean age of female patients were 35.8 +/- 9.5. The mean age of the total study population is 38.6 +/- 10. This table shows that the mean age of male and female sub groups were comparable and the difference is not statistically significant

Comparative analysis of the initial and follow up CD4 count in male subjects

CD4 count	Male	
	Initial	Followup
0-100	21	4
100-200	14	7
200-300	4	12
300-400	2	12
400-500	2	4
500-600	0	2
600-700	0	2
700-800	0	0
Total	43	43
Mean	133.7	294.2
S.D	108.9	148.5
Z	5.7	
Significance	P < 0.0001	

In the male subgroup the mean CD4 count at the time of presentation is 133.7 and the mean CD4 count after follow up is 294.2.In this table the mean CD4 count before and after therapy were compared and the difference is statistically significant (P < 0.0001)

Comparative analysis of the initial and follow up CD4 count in female subjects

CD4 count	Female	
	Initial	Followup
0-100	8	1
100-200	3	1
200-300	1	3
300-400	0	4
400-500	0	0
500-600	1	2
600-700	0	1
700-800	0	1
Total	13	13
Mean	126.9	373.1
S.D	142.3	200.6
T	3.609	
Significance	P < 0.01	

In the female subgroup the mean CD4 count at the time of presentation is 126.9 and the mean CD4 count after followup is 373.1.In this table the mean CD4 count before and after therapy were compared and the difference is statistically significant

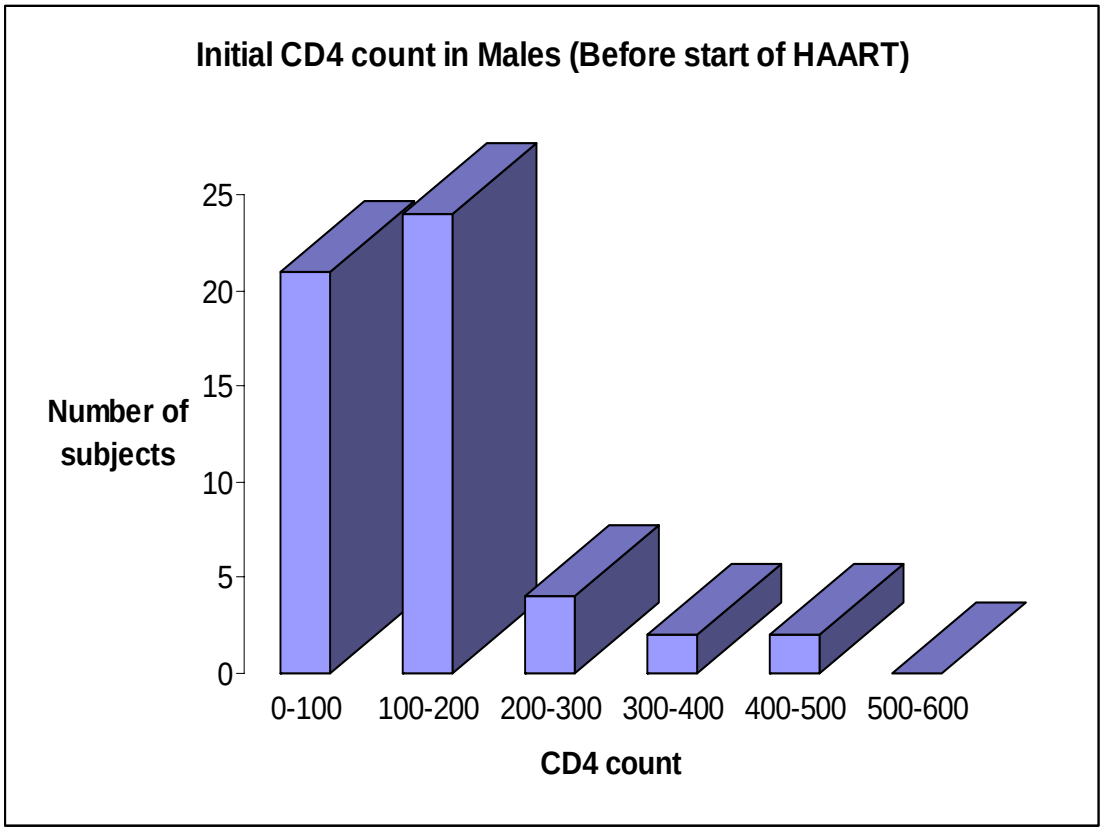
(P < 0.01)

Comparative analysis of the initial and follow up CD4 count in total subjects

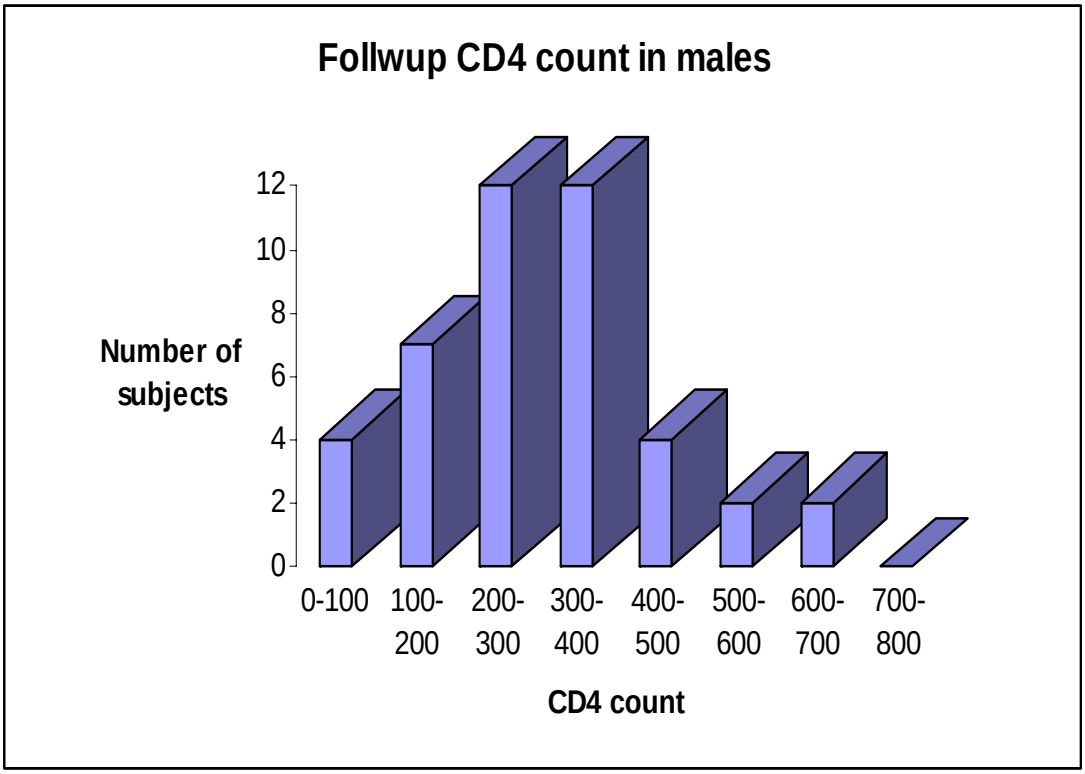
CD4 count	Total	
	Initial	Folloup
0-100	29	5
100-200	17	8
200-300	5	15
300-400	2	16
400-500	2	4
500-600	1	4
600-700	0	3
700-800	0	1
Total	56	56
Mean	132.1	312.5
S.D	116.2	163.5
Z	6.7	
Significance	P < 0.0001	

In total, the mean CD4 count at the time of presentation is 132.1 and the mean CD4 count after followup is 312.5.In this table the mean CD4 count before and after therapy were compared and the difference is statistically significant (P < 0.0001)

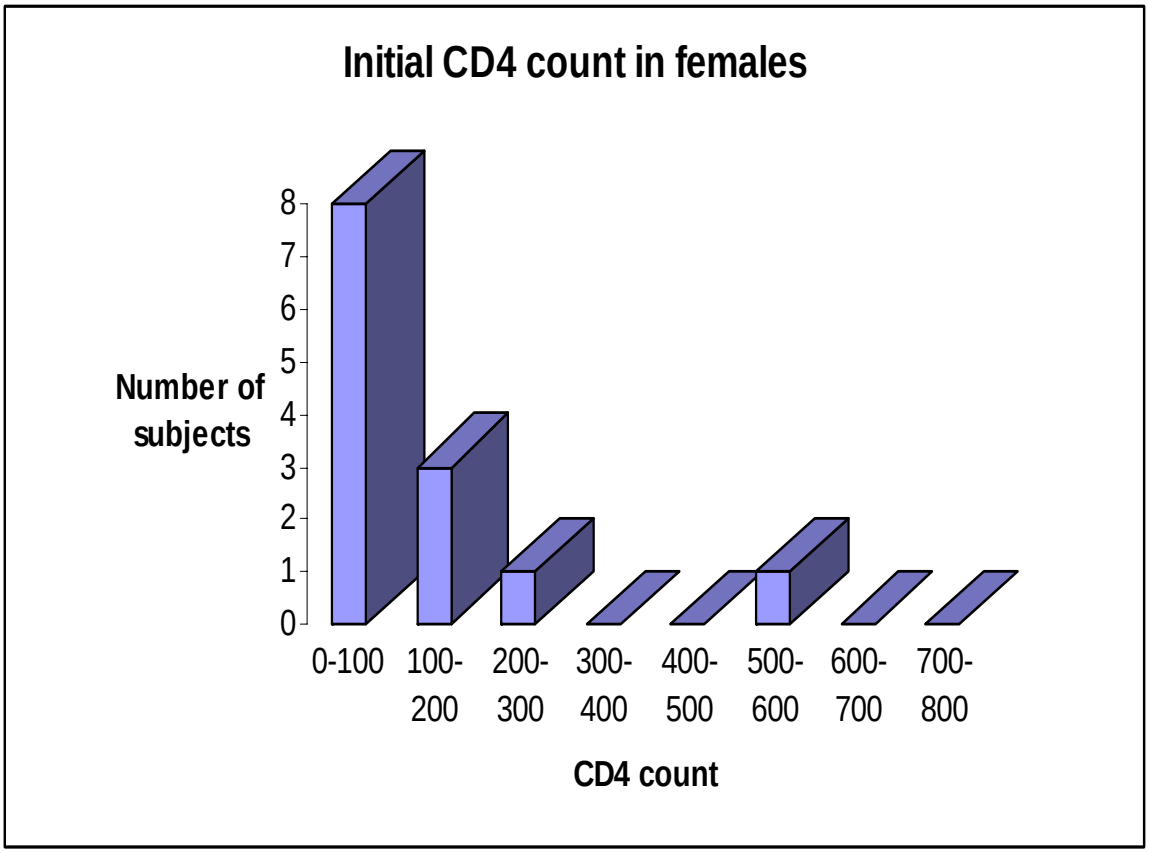
Bar diagram showing Initial CD4 count in males



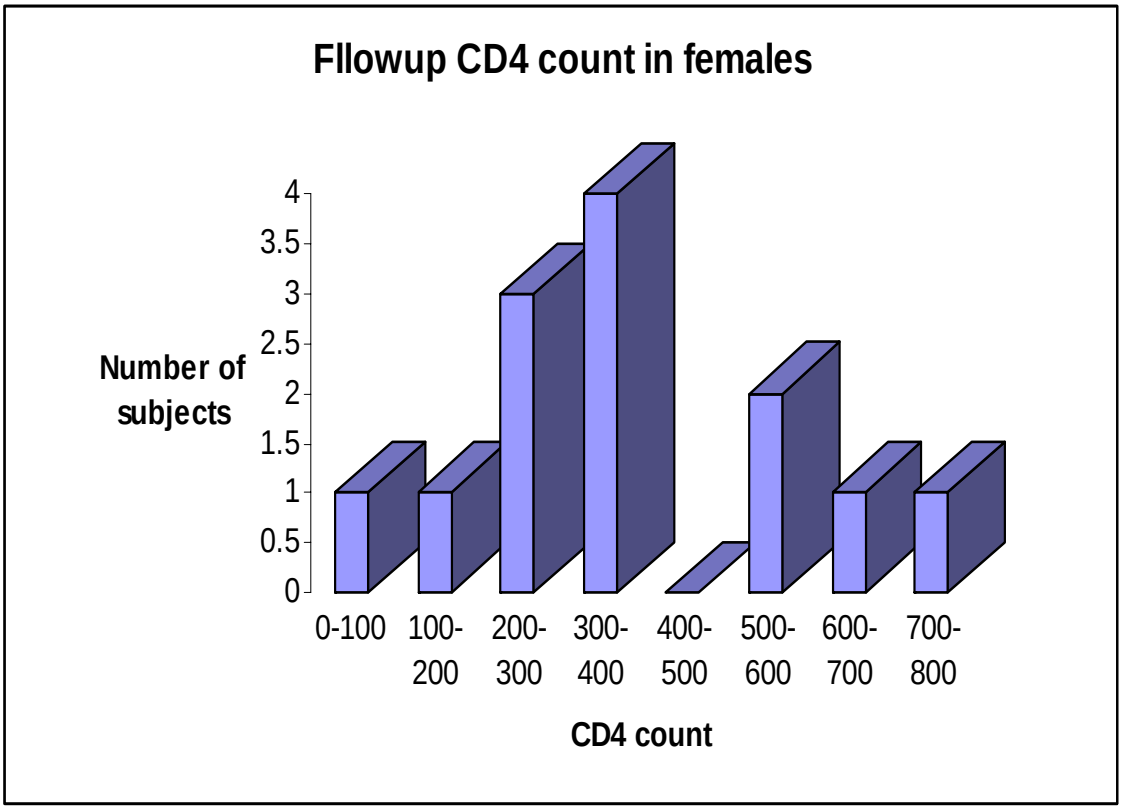
Bar diagram showing follow up CD4 count in males



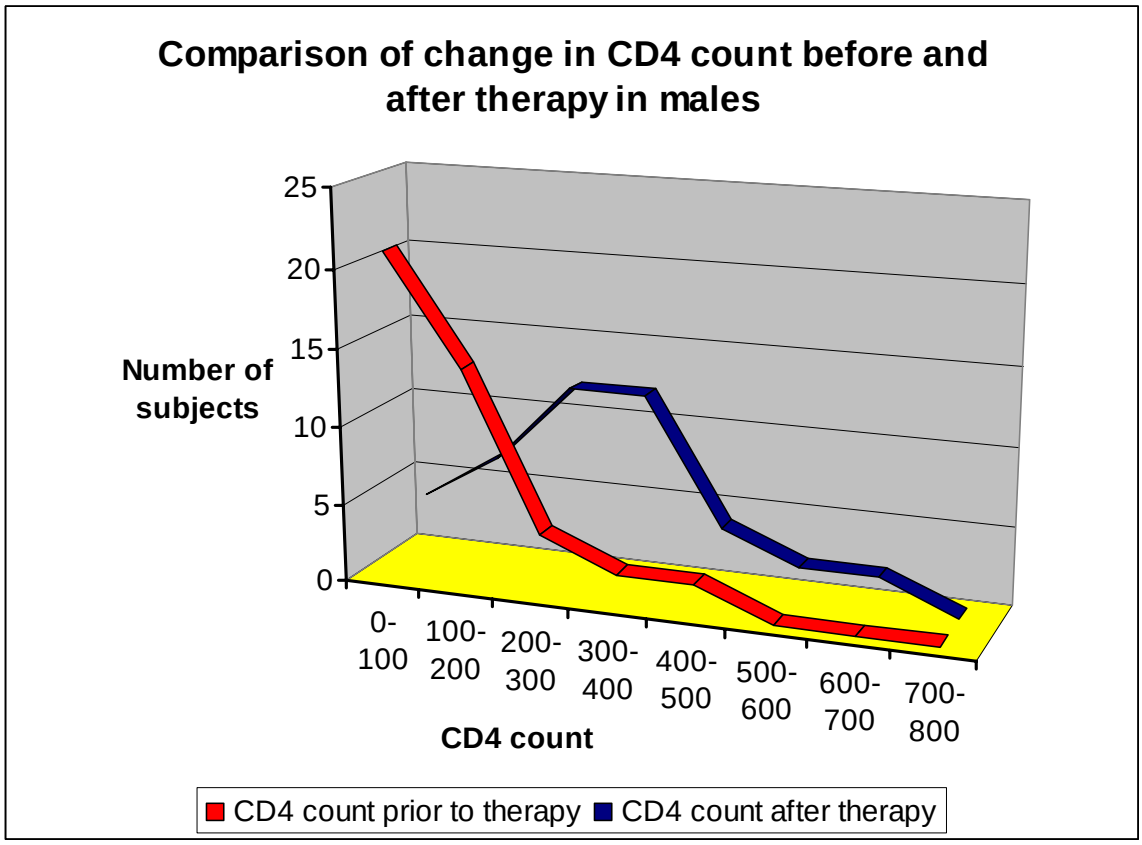
Bar diagram showing Initial CD4 count in females



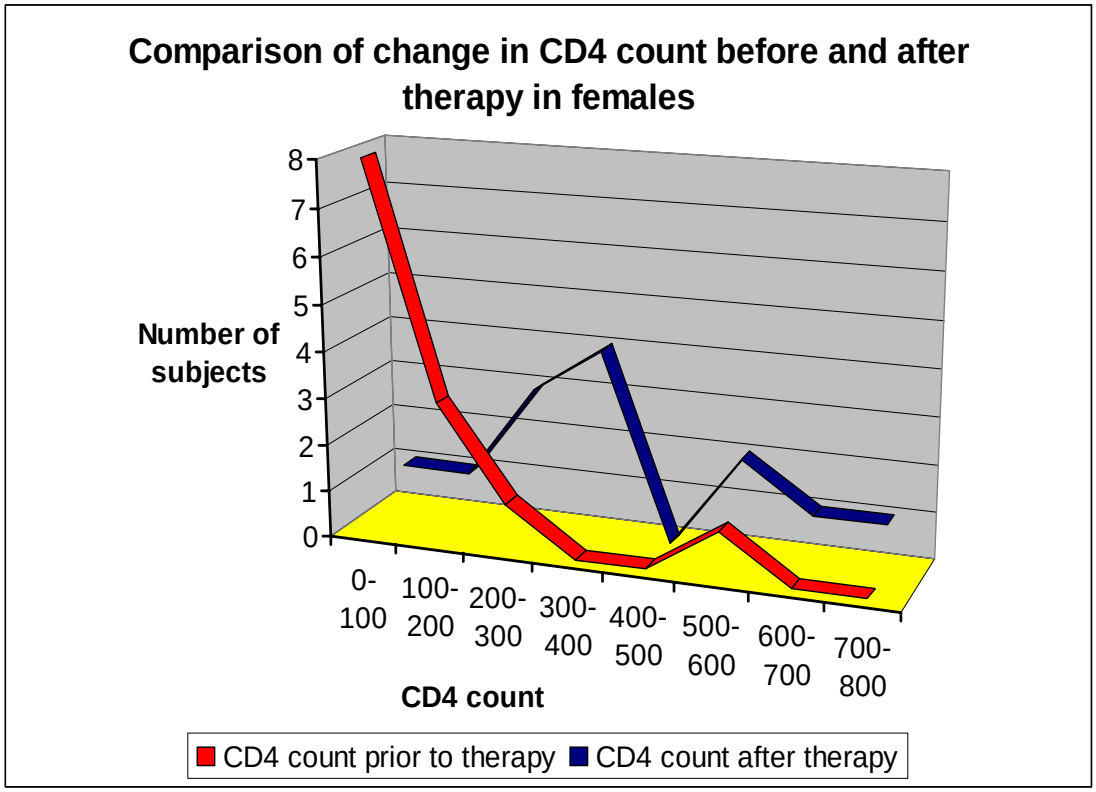
Bar diagram showing follow up CD4 count in females



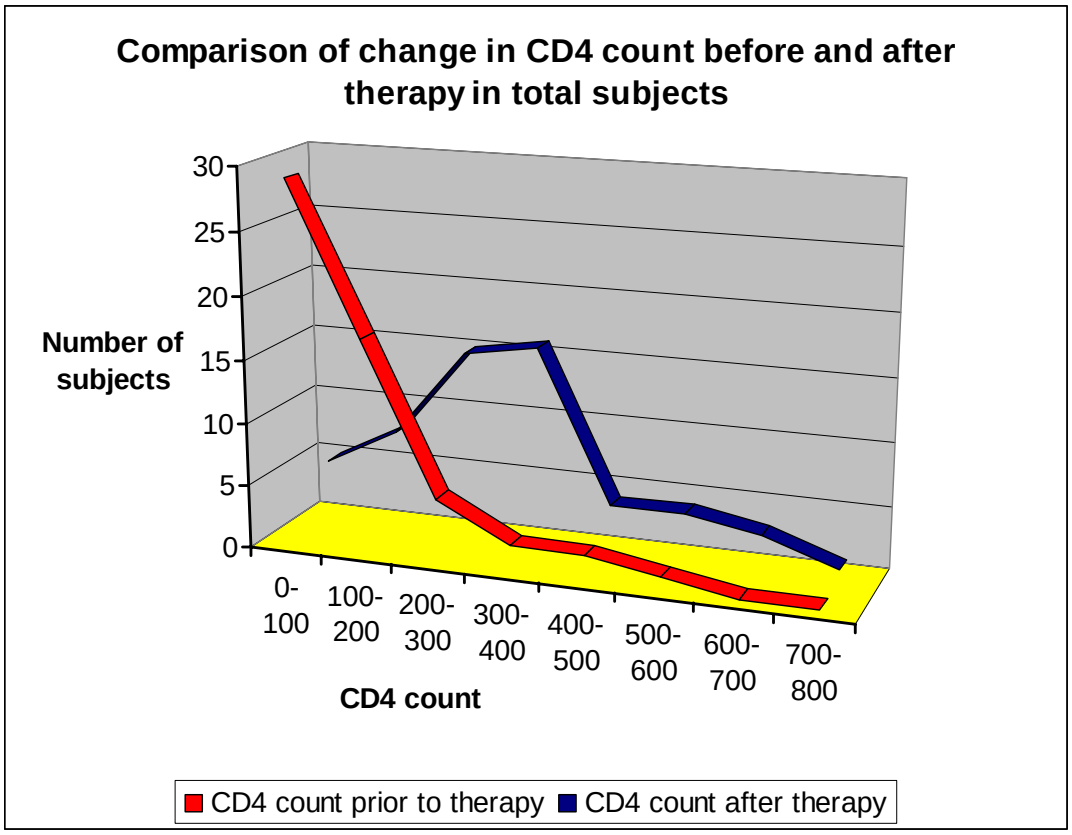
Comparison of change in CD4 count before and after HAART in males



Comparison of change in CD4 count before and after HAART in females



Comparison of change in CD4 count before and after HAART in total subjects



DISCUSSION

DISCUSSION

The Current study aimed at finding the correlation between CD4 count and HAART and the change in CD4 count after HAART. However there were sex related change in the subjects with respect to age. The change in CD4 count in the total subjects without doubt has been noticed. The difference between the male and female subjects was not statistically significant and the overall increase is seen in both sexes.

Most of the previous studies evaluated the increase in CD4 count with relation to sex and also to viral load. With the available resources the study involves both the sex correlation and independently.

Most of the patients seeking medical therapy fall in a range of low CD4 count between 0 – 100.The clinical and epidemiological importance of this finding is important for the patients and therapists.

The clinical importance of HAART is related to its impact on the CD4 count as well as the well being of the patient.

In this study it was found that the mean age of seeking medical advice is between 36.1 – 41.1 years.

There is no sex difference in presentation of the disease ($p > 0.05$) .The reason for this could be due to the disease awareness in both the sexes. Another cause that can be attributed could be the down regulation of the immune system with advancing age and the subjects above 50 year age group are low in number when compared to younger age groups.

From the statistics it understood that the mean CD4 count at the time of presentation was 133.7 in males and 126.9 in females. This when compared to the normal CD4 count is much less. It is also noted the subjects presenting with a very low count initially , after HAART show improvment in the CD4 count and the magnitude of the opportunistic infections.

The mean increase of the count when the total subjects are taken is also significant (Z – 6.7). The mean count after therapy was 294.2 in males and 373.1 in females. There is a moderate difference in the increase of cells between the sexes can be noted.

Even though the initial count is very low in females when compared to males the response to HAART is good for females than in males. The males also show a rise in count but not to the extent of females. Castagna et al in their study showed that sopping HAART resulted in gradual decline in the number of CD4 cells. However this study does not include the individuality of antiretroviral drugs. The drugs used are combinations of individual agents.

While analysing the data it can be known that the number of subjects in the 0 -100 CD4 count group initially showed good response to therapy.

There are also decline in the number of cells in few subjects. It can be noted that these subjects presented with very low CD4 count at the beginning.

These findings show the definitive impact of HAART in increasing CD4 cells in AIDS patients.

CONCLUSION

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Majority of the AIDS patients present with a low CD4 count especially the females.

The females show a dramatic improvement in the CD4 count after HAART when compared to males eventhough they present with a very low count initially

The mean age of presentation of the disease for both males and females is around 37 years

There is a definite increase in the CD4 cell count after initiation of HAART.

LIMITATIONS OF THE STUDY

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This study does not take into account the existence of the opportunistic infections at the time of presentation and in the course of therapy.

This study does not include children.

The study does not include the change in CD4 counts within six months after institution of HAART

SUMMARY

SUMMARY

The presentation of AIDS occurs commonly in the middle age group. The females are presenting with a very low CD4 count initially. However the response to HAART is much higher in females than in males and above all that the institution of HAART has major influence on CD4 counts by increasing the number. The counts increase from an abnormal low level to acceptable levels.

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